POLYCYTHEMIA VERA—ITS COURSE AND TREATMENT: RELATION TO MYELOID METAPLASIA AND LEUKEMIA*

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POLYCYTHEMIA vera or erythremia is a chronic progressive disease of insidious onset. It is characterized by an initial absolute increase in the number of erythrocytes which usually is accompanied by a leukocytosis, thrombocytosis, splenomegaly and ruddy cyanosis.

PATHOGENESIS

Theoretically, erythrocytosis may occur because of increased production of red cells, decreased erythrocyte destruction or a combination of both. The presence of polychromatophilic erythrocytes and occasionally normoblasts in the peripheral blood together with an erythroblastic hyperplasia in the bone marrow is strong evidence favoring increased erythrogenesis as the cause of the polycythemia. More definitive evidence for increased red cell production has been obtained by the use of radioactive iron[1,2] and isotopically labelled glycine.[3] Utilizing N_{15}, London et al. have shown that the erythrocytosis of polycythemia vera is due not to the production of red cells of increased longevity but rather to a two- to three-fold increase in the production of normal red cells and hemoglobin by the hyperplastic bone marrow.[3]

Since the original description of the syndrome by Vaquez[4] and its subsequent clinical delineation as a specific disease entity by Osler,[5] speculation has centered around the cause of the increased erythropoiesis. The early appreciation of the relation of the anoxemia of high altitude to erythrocytosis[6] and the polycythemia secondary to congenital heart disease and pulmonary conditions, has directed attention to bone marrow anoxia as the fundamental stimulus in erythremia. The production of this marrow anoxemia has encompassed many theories (Table I). An analysis

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TABLE I—SOME OF THE MOST COMMON THEORIES OF THE ETIOLOGY OF POLYCYTHEMIA VERA.

A. Increased red cell production
   I Anoxemia
      a) Anoxic
         Impaired pulmonary diffusion; vasoconstriction; increased tissue respiration
      b) Anemic
         Abnormal hemoglobin
      c) Stagnant
         Extreme capillary dilatation; sclerosis & fibrosis of marrow capillaries
      d) Competitive
         Myeloid hyperactivity
   II Humoral
      a) Excess intrinsic factor (Addisin); Hemopoietine
   III Hormonal
B. Decreased red cell destruction
      a) Increased life span of RBC
C. Neoplastic

of this multitude of theories relating to the etiology of erythremia and including anoxemia, hormones, humoral substances, neurogenic stimuli and others[7-10] is beyond the scope of this paper. Certain comments regarding the blood and bone marrow oxygen may be warranted, however.

No satisfactory evidence has been produced as yet substantiating any of these ingenious hypotheses leading to bone marrow anoxia. Rather, the bulk of the evidence suggests that anoxia per se is not the primary stimulus for the development of the erythrocytosis in erythremia. Definitive studies of the oxygen saturation of the bone marrow obtained by sternal aspiration by Schwartz and Stats,[11] and Berk and co-workers,[12] have shown either normal or increased oxygen saturation values in polycythemia vera. In the erythrocytosis secondary to anoxemia, leukocytosis, thrombocytosis and splenomegaly do not occur. The minimal oxygen unsaturation occasionally found in erythremia is probably of no significance in the production of the hypervolemia and the impaired pulmonary diffusion sometimes found in polycythemia vera[8] is rather an effect and not a cause of the erythrocytosis.

Because of its insidious onset and prolonged duration one is presented with a rare opportunity to study a disease throughout its complete course.[13] Only by an appreciation of the various developmental potentialities of erythremia can one intelligently theorize on the fundamental abnormality in this disease and its pathogenesis. Lawrence[14] and Wiseman and his co-workers[15] have emphasized the paucity of follow-up care in any large series of cases, studies on the whole being confined to only a small segment of the slowly developing syndrome. In the usual definition of the disease one is constantly reminded of the erythrocytosis that is invariably present, yet too few statements are made concerning the fact that this increased red cell mass may occur only during the initial phase of the disease and may even go undetected.

Within a few years following the original description of polycythemia vera, Türk[16] noted the frequent occurrence of granulocytic leukocytosis and the presence of immature red and white cells in the peripheral blood of patients with erythremia. He postulated an overactivity of the leukopoietic as well as the erythropoietic tissue, due to a primary hyperplasia of the marrow. The term erythremia was suggested to distinguish this disease from erythrocytosis secondary to anoxemia.

The concept of a total panmyelosis with expansion of the active red marrow to encompass the total potential marrow space received increasing support from biopsy and post-mortem examinations of the marrow in early erythremia; the frequent association of leukemoid and leukemic blood pictures, in some series running as high as 30 per cent,[14, 17] the occurrence of immature red and white cells in the peripheral blood and the thrombocytosis lend support to the hypothesis that erythremia is a chronic generalized bone marrow disease.

As cases of polycythemia vera were followed over a prolonged period of time, it was noted that the erythrocytosis was merely an initial facet of a complex disease process. This disease frequently terminated in leukemia, osteosclerosis, myelofibrosis, myeloid metaplasia and other diverse pathological entities. The concept of the neoplastic nature of erythremia thus arose and the disease now is becoming recognized as having a similar origin as other myeloproliferative syndromes.[18-21] Against the neoplastic nature of erythremia has been the relatively prolonged course of the disease and the apparent lack of invasiveness manifested by the proliferating cells. However, well differentiated malignant cells are functionally close to normal cells and may have a benign course for

many years.[22] Wiseman[23] has noted that "in a blood cell strain, it is only the cell in the end-stage of maturation that regularly shows appreciable and visible quantitative increase under conditions of stimulation, not the precursor cell."

An appreciation of the protean pathological findings seen in polycythemia vera of long duration has crystallized an evolutionary pattern that encompasses all the variations seen. It has long been obvious that stimulation of a particular hematic cell series in the marrow often induces a reactive response in the other hematic cellular components, e.g., following hemorrhage, not only is there a hyperplasia of the red cell series but of the white cells and platelets as well. Erythroleukemia shows proliferation of both the erythroid and myeloid marrow precursors, and stimulation of the megakaryocytes with extreme thrombocytosis is not infrequent in myeloid leukemia.

It appears that the marrow cells may proliferate as an hematic unit,[19] the clinical and pathological picture depending upon the degree of the stimulus transmitted along any specific cellular line. This concept of total marrow hyperplasia in response to a stimulus implies an antecedent proliferative stimulus exerted on the precursor cell or cells of the differentiated hematic cells. One may therefore consider an initial growth stimulus directed at the primitive mesenchymal or reticulum cell from which all embryonal and adult blood cells as well as fibroblasts and osteoblasts are formed and then, in varying degrees, specific stimuli directed toward special cellular compartments (Fig. 1).

In the embryo blood cell formation occurs not only in the bone marrow but in extra-osseous organs as the liver and spleen. Localization of hemopoiesis to the marrow cavity shortly before birth results in a physiologic regression of these heteroplastic foci derived from the cytoplasmic reticulum. Nonetheless, these sites retain their potential functional capacity to produce differentiated hematic cells when stimulated.[21,24] Klemperer[21] has noted that "stimulation of the undifferentiated mesenchyme may lead to local or generalized proliferation" with specific cellular differentiation generally occurring. The common denominator of the adult functioning bone marrow and the potential extra-osseous marrow in the liver and spleen is the undifferentiated mesenchyme or cytoplasmic and fibrillar reticulum.[21] Presumably then, a stimulus directed at the reticulum in the marrow will simultaneously produce a like response in the dormant extra-osseous mesenchymal cell. The resultant

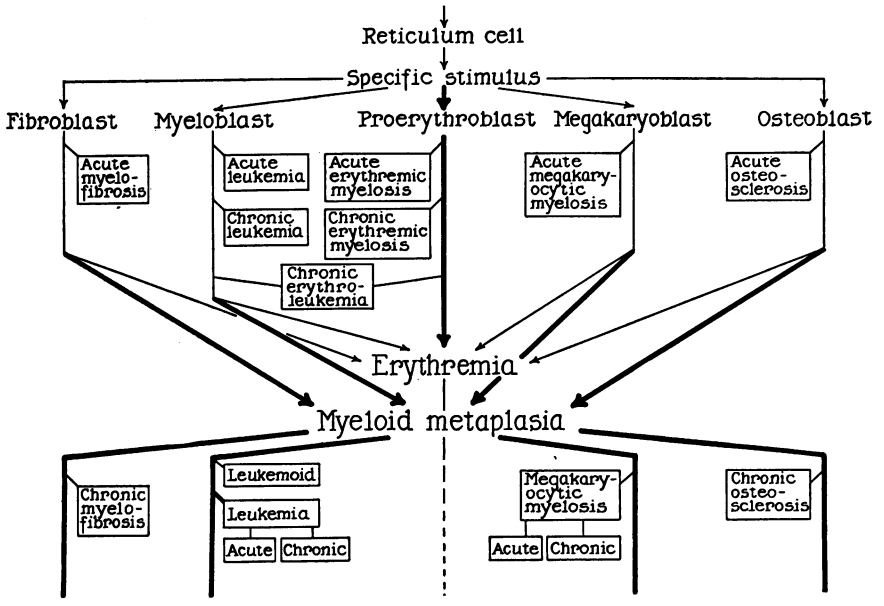

Figure 1: Schematic concept of the interrelationship of polycythemia vera (erythremia) with myeloid metaplasia and other proliferative diseases of the reticulum. Stimulation of the primitive reticulum cell must be hypothecated to account for the proliferation of all hematic and non-hematic mesenchymal derivatives occurring in polycythemia vera. Qualitative and quantitative variations in the intensity of the stimuli will determine the hematologic and pathologic changes occurring during the course of erythremia, e.g., megakaryoblast stimulation to produce thrombocytosis or megakaryocytic myelosis and stimulation of the white cell precursor to produce a leukemoid or leukemic picture. Fibroblastic and osteoblastic hyperactivity may result in myelofibrosis or osteosclerosis ("spent polycythemia"). Erythremia and myeloid metaplasia are closely related, the latter probably always associated with erythremia of sufficient duration. With development of extramedullary hematopoiesis, erythrogenesis may diminish as denoted by the dotted line whereas other specific stimuli appear to grow more intense (heavy lines). Myeloid metaplasia may occur without antecedent erythremia, the erythrogenetic stimulus initially appearing normal or diminished, whereas the other stimuli are increased from the onset (note heavy lines bypassing erythremia). The hematologic and pathologic picture in myeloid metaplasia associated with polycythemia vera of long duration and that of the idiopathic variety are indistinguishable. (Modified from Rosenthal, M. C.,[24] *Bull. New England Med. Center 12*:154, 1950.)

pathological picture will depend on the locus of the stimulated cells and the qualitative and quantitative nature of the stimulus, whether along hematic, fibroblastic or other lines of development and whether it be an acute or chronic disorder. In polycythemia vera the initial fundamental disturbance may very well be a reticulosis and the extramedullary blood formation which always accompanies polycythemia vera of a sufficiently long duration is probably of autochthonous origin and is not compensatory.[24]

A concept such as this offers an attractive hypothesis for the numerous transitional clinical and pathological findings frequently encountered in polycythemia vera, leukemia, myelofibrosis, osteosclerosis and associated syndromes. The quantitative variation in simultaneous stimuli occurring over a period of months or years will produce disease forms that have as the only abnormality common to all, pathological cell proliferation. This concept is graphically illustrated in Fig. 1. A hypothetical growth stimulus acting on the undifferentiated mesenchymal cells may produce one or more specific stimuli acting simultaneously but quantitatively different. Thus, the acute syndromes are usually manifested along one potential line of development, show invasive, disorganized, neoplastic tendencies of the proliferating cells and are rapidly fatal. Even in the acute syndromes the appearance of two or more simultaneously stimulated cellular categories may occur. In the few cases of acute erythremic myelosis studied by us, although initially the bone marrow and peripheral blood were predominantly erythro-normo-blastic, these patients always died with the characteristic blood and marrow findings of acute myeloblastic leukemia. It would appear that the erythrogenetic stimulus eventually spent itself or was transformed and a myeloblastic one prevailed terminally. In chronic leukemia the stimulus may not be as intense and may be accompanied by erythroid hyperactivity resulting in a picture of erythroleukemia; a more pronounced erythrogenetic stimulus might produce a picture of chronic erythremic myelosis (Fig. 1). Simplification of this chart to include only the more important syndromes should not eliminate the fact that other lines of development may simultaneously undergo increased proliferative activity.

In the case of erythremia the stimulus to erythropoiesis initially predominates, although simultaneous stimulation of the granulocytic and platelet precursor cells produces the leukocytosis and thrombocytosis usually a part of polycythemia vera. Non-hematic increased cellular activity in the fibroblasts and osteoblasts also occurs with fibroblastic and osteoblastic as well as reticulum cell proliferation, the latter being more obvious in the spleen. The initial stimulus must also be qualitatively different in this disease, since the development of all cells is along rather orderly lines. The bone marrow and peripheral blood reflect the generalized hyperactivity with panmyelosis of the marrow (Fig. 2), and immature red and white cells and increased platelets in the peripheral blood.

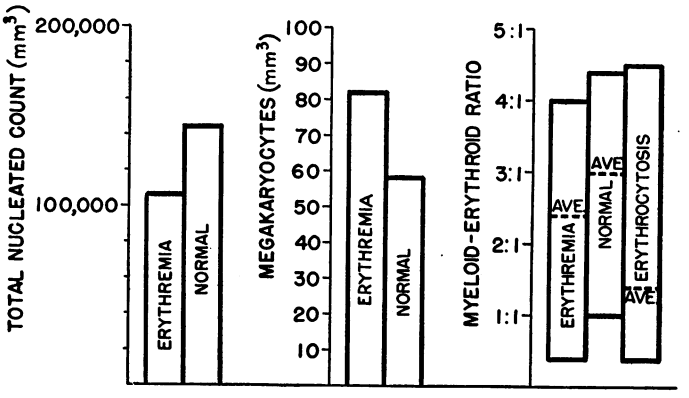

Figure 2: Average bone marrow results in normal patients and 131 cases of polycythemia vera before treatment contrasted with erythrocytosis (secondary polycythemia). The questionable reduction in total nucleated count and the slight increased megakaryocyte concentration in the bone marrow of erythremia are accompanied by a decreased M:E ratio (ave. 2.5:1 range 0.5-4:1). Because of extreme overlapping in all groups however marrow aspiration findings are rarely helpful as a diagnostic aid.

The extra-osseous potential marrow space appears to undergo the same proliferative activity and the liver and spleen become enlarged due to hyperplasia of the cytoplasmic and fibrillar reticulum. The occurrence of myeloid metaplasia during a period of hyperplasia in the bone marrow seems to negate the concept of compensatory heteroplastic blood formation. Accordingly, erythremia and myeloid metaplasia go hand in hand. Our cases of erythremia of long duration have invariably shown some degree of myeloid metaplasia in the liver and spleen with varying fibrosis in the marrow at autopsy. With sufficient passage of time, changes begin to appear in erythrogenesis. Red cell formation begins to falter and other lines of development appear to gain ascendency. Thus the phase of polycythemia vera with so-called polynuclear cell leukemia or the syndrome of myelofibrosis may appear. In other cases the megakaryocytes predominate with the resultant picture of acute or chronic megakaryocytic myelosis; still others display hyperactivity of the osteoblasts and bone formation encroaches upon or completely replaces the marrow activity, analogous to the fibrous tissue of myelofibrosis. At this phase of the disease one may see a severe anemia, a leukemoid or leukemic blood picture, thrombocythemia or thrombopenia all in a patient who a number of years before had a severe polycythemia.

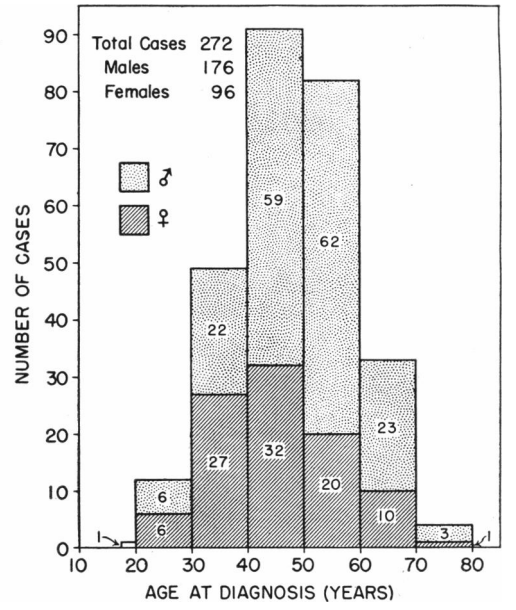

Figure 3: Age and sex distribution in 272 cases of polycythemia vera. The average age at the time of diagnosis was 48.1 years with a male to female ratio of 1.8:1.

This dynamic concept brings together the multitude of variegated names and syndromes representing one common disease entity, erythremia.

Myeloid metaplasia and myelofibrosis need not necessarily be associated with polycythemia vera but may be idiopathic in type. Of sixty-one cases of myelofibrosis with myeloid metaplasia studied by us,[25] eight (13 per cent) instances occurred in known polycythemics who had been followed in our clinic, fifteen (25 per cent) had histories and laboratory findings before admission to the hospital typical of erythremia, and twelve (20 per cent) had histories suggestive of polycythemia vera but no correlative laboratory data. Thus thirty-five or 58 per cent of sixty-one cases of myeloid metaplasia with myelofibrotic marrows had a probable antecedent polycythemic phase and 42 per cent were apparently idiopathic. Presumably, in the idiopathic variety not preceded by erythremia, erythrogenetic activity remains normal or is suppressed at a very early phase of the disease while hyperactivity of the other hematic and fibroblastic components occurs. With this above pathogenetic concept

TABLE II—LABORATORY AND CLINICAL FINDINGS IN POLYCYTHEMIA VERA

A. LABORATORY
1. Erythrocytosis
2. Granulocytic leukocytosis
3. Thrombocytosis
4. RBC & WBC immaturity
5. Panmyelosis
6. Red cell volume increased
*7. Oxygen saturation normal
8. Plasma iron turnover increased
9. Red cell iron turnover increased
10. Blood pigments normal

B. CLINICAL
1. Symptoms
   a) Cardiovascular
   b) Neurologic
   c) Gastrointestinal
   d) Hemorrhagic
2. Plethora
3. Hepatomegaly
4. Splenomegaly
5. Cardiac normal; pulmonary normal

*The arterial oxygen saturation is the only test capable of differentiating between polycythemia vera and erythrocytosis secondary to anoxemia.

of polycythemia vera and myeloid metaplasia the clinical course of the disease may be more comprehensible.

COURSE

Polycythemia vera is primarily a disease of middle age with an average age at diagnosis in our group of cases of 48.1 years and ranging from eighteen to seventy-nine years. The distribution of cases in males to females is 1.8:1 a ratio in accord with other reports[14,17,26] (Fig. 3).

The course of polycythemia vera is one of many years' duration in the satisfactorily treated case. A normal life expectancy for persons in this age group is about sixty-eight years,[14] and in those cases of erythremia carefully followed and successfully treated, this life expectancy may be attained and exceeds that for pernicious anemia or diabetes.[27]

There is an asymptomatic developmental phase, the duration of which must remain conjectural although Dameshek has ascribed a period of about five years for this.[28]

Subsequently, during the stage of erythrocytosis lasting from five to twenty years with its myriad of symptoms referable primarily to the hypervolemia and pancytosis, the diagnosis is usually made (Table II). Many patients may remain asymptomatic during this period[29] despite the abnormal pancytosis and the diagnosis may be made only during a fortuitous routine examination.

Polycythemia vera does not signify only a hypervolemic phase however. The disease progresses inexorably through its cycle, producing one picture at one time and another hematic response may prevail at another. A period of relative normalcy as far as the red cells are concerned may follow the polycythemic stage producing the so-called remissions that have been reported.[28,29] This phase should be looked upon as the first sign of diminished erythropoietic activity in the marrow and the early development of the syndrome of myeloid metaplasia. Careful examination of the blood and marrow at this time will show a relatively normal red cell concentration with a leukocytosis and thrombocytosis. The blood smear shows a leukoerythroblastic blood picture with a few myelocytes and normoblasts.[19,20,30] The red cells, particularly, are characteristic of the developing metaplastic blood formation, there being polychromatophilia and marked aniso- and poikilo-cytosis with microcytes, elliptical cells, "teardrop" cells and other bizarre red cell forms. These red cell changes are characteristic of either this stage of polycythemia vera or of the idiopathic type of myeloid metaplasia. It is not unusual to have a marked granulocytic leukocytosis at this time with a thrombocytosis of one or two million featuring abnormally large platelets or even megakaryocytic fragments in the blood. The so-called polynuclear cell leukemia probably falls into this group of early myeloid metaplasia. The marrow still may be hyperplastic but instead of showing a panmyelosis it now shows some reduction in the erythropoietic elements with an increase in the myeloid cells, the fibrillar and cytoplasmic reticulum and megakaryocytes. The erythroid foci appear to be reduced due to the encroachment by other hyperactive cellular components. Whether this is due to degeneration of the red cell precursors with replacement by other cellular systems or is due to increased stimulation and hyperactivity of the white cells, fibroblasts and megakaryocytes is not known. Simul-

taneously with the marrow changes, the spleen enlarges and becomes the site of extramedullary blood formation. A splenic puncture done at this time or subsequently will show a picture similar to that seen in the marrow with reticulum cell hyperplasia and hematic cell proliferation, the findings of myeloid metaplasia[31] (Fig. 4).

The changes in the marrow and spleen proceed unchecked with marrow proliferation of fibroblasts and increasing encroachment upon the erythroid tissue. It must be remembered that although hematic cell activity diminishes in varying degree, the marrow still remains the site of extreme proliferative activity. Fibrosis and osteosclerosis merely signify that the stimuli, spent as far as the red cells are concerned, now show increasing activity toward the other hematic cells as well as toward the non-hematic mesenchymal derivatives, the fibroblasts and osteoblasts. The early spent phase is thus merely a later stage in the naturally determined course of the disease. The red cell activity may be gradually relocated to extramedullary sites (Fig. 4) and because of the abnormal forms produced, anemia may become prominent. These red cells from extra-osseous sites have been shown to have a shortened survival[32] but if extra-osseous formation is great enough, anemia may be mild or even absent and a compensated myelofibrotic state may be seen that may last for months or years. The marrow eventually becomes almost completely fibrotic with megakaryocytes now prominent due to disappearance of most of the other cellular elements; reticulum cells, osteoblasts and a few white cells may remain. At this stage one encounters a "dry tap" on marrow aspiration and the peripheral blood shows anemia, leukopenia and a variable platelet count although thrombocytopenia is usual (Fig. 4). Other developmental possibilities remain in that with the progression of the disease white cell hyperactivity may predominate resulting in a terminal picture of myeloid leukemia. In some cases the degree of megakaryocytic hyperactivity may be such that the condition has been called megakaryocytic leukemia or myelosis; in others, megakaryocytic, myelocytic, fibroblastic and osteoblastic activity may all be stimulated to produce complex clinical and post-morten findings.

Complications and Treatment

The treatment of chronic diseases of unknown etiology should be directed toward symptomatic relief as well as correction of the altered physiologic state for as long a period of time as possible. It follows that

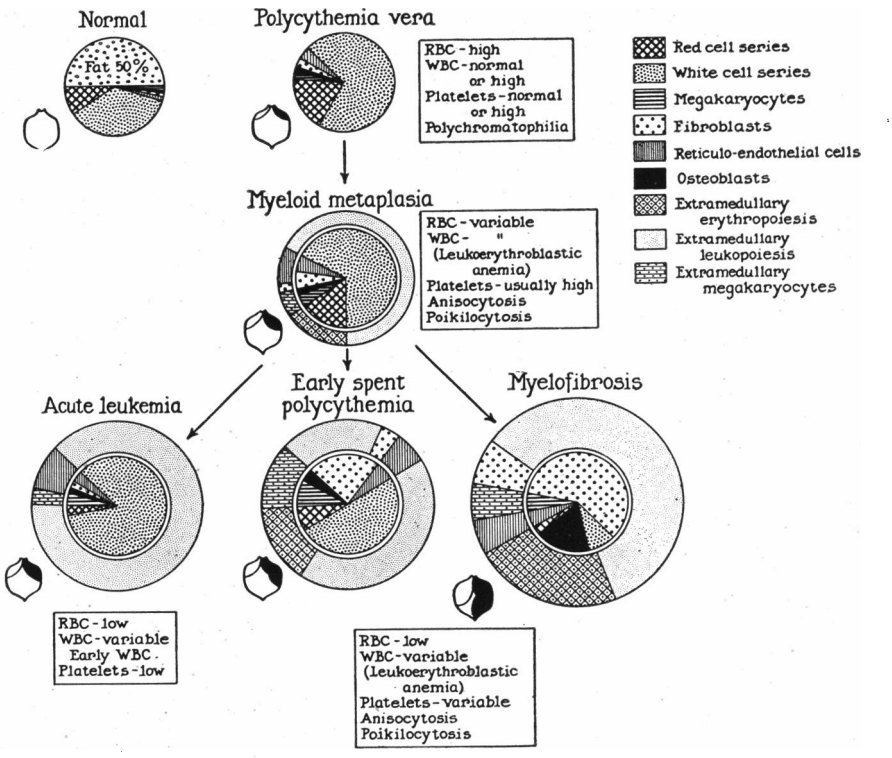

Figure 4: Hypothetical concept of the course of polycythemia vera. The blood, bone marrow and extra-osseous potential marrow, considered "the blood tissue," reflect simultaneous changes occurring during the course of polycythemia vera. In polycythemia vera the hyperplastic marrow expands to encompass the total marrow space at the expense of the fat cells. There is a panmyelosis with stimulation of all hematic and non-hematic cellular derivatives of the reticulum cell. Blood examination reveals an erythrocytosis and usually a granulocytic leukocytosis, thrombocytosis and immature red and white cells. Splenomegaly and hepatomegaly are frequently present, initially due to the increase in blood volume but subsequently associated with reticulum cell hyperplasia and heteroplastic blood formation. With continued hyperactivity the dormant extra-osseous potential marrow becomes functionally active and the site of extramedullary hematopoiesis (stage of myeloid metaplasia) as the spleen and liver enlarge (outer circle designates extramedullary blood formation). The bone marrow shows diminution in erythrogenesis and proliferation of reticulum cells, fibroblasts, megakaryocytes and white cells. The peripheral blood mirrors the marrow changes with usually a mild to moderate anemia although normal values (compensated state) may prevail for many years. Thrombocytosis is common as is a leuko-erythroblastic blood picture. With time, progressive changes in cellular composition of the marrow occur (stage of early spent polycythemia). Fibroblastic or osteoblastic proliferation encroaches on hematic cell activity with a reduction particularly in erythropoiesis. Megakaryocytes appear more plentiful due either to increased proliferative activity or a quantitative decrease in other hematic cells. The liver and spleen, the site of extramedullary hematopoiesis, are not encased in bone, hence can expand markedly. There is now a leukocytosis and thrombocytopenia or thrombocytosis, leuko-erythroblastic anemia with morphologically bizarre red cells. Further fibroblastic or osteoblastic proliferation may obliterate the marrow cavity with all blood formation occurring in the extra-osseous marrow (stage of myelofibrosis). Note that nonhematic cell proliferation occurs in the liver and spleen also. The anemia becomes more severe with usually a leukopenia, thrombopenia and a more marked leuko-erythroblastic blood picture. Hepatosplenomegaly may be tremendous. This phase of myelofibrosis (myeloid metaplasia) may be a terminal picture in polycythemia vera. Other lines of proliferation may gain ascendency, e.g., the white cells, with development of an acute leukemia occasionally preceded by a stage similar to chronic myelocytic leukemia; megakaryocyte hyperactivity may result in so-called megakaryocytic myelosis, etc.

Acute leukemia, spent polycythemia and myelofibrosis are all depicted as stemming from a common stage of myeloid metaplasia. Variation in proliferative activity of any combination of cellular categories may produce complex clinical and pathological syndromes. Thus, well developed myelofibrosis may frequently show large numbers of myeloblasts and myelocytes in the blood and, similarly, a terminal acute blastic leukemia may show extensive fibroblastic proliferation. (The area represented for any specific cellular series is only approximate and merely represents an attempt to demonstrate graphically a few of the multiple developmental potentialities in polycythemia vera.)

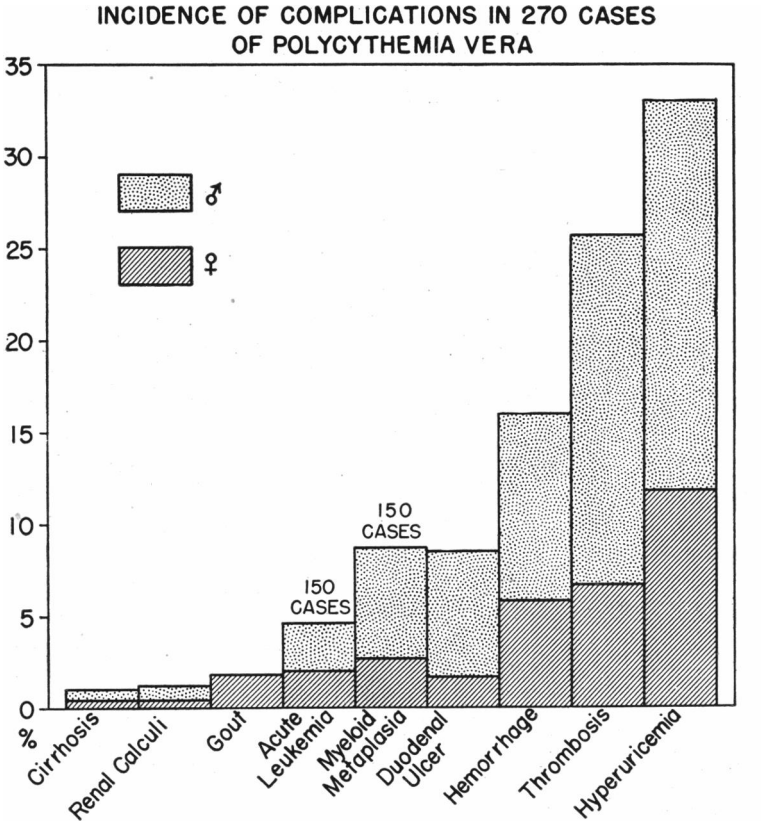

Figure 5: Incidence of complications in 270 cases of polycythemia vera. The data of only 150 cases could be utilized for determining the per cent incidence of acute leukemia and myeloid metaplasia. These latter should not be classified as complications since they are stages in the course of polycythemia vera.

comfort to the patient, ease of administration of the therapy, reduction in complications and morbidity and return to a normal social and economic status for the patient should be achieved if possible with the therapeutic method employed.[14, 15, 17, 27]

The symptoms and complications of erythremia are directly related to the increased blood volume and viscosity, and the panmyelosis (Fig. 5). Sufficient data have been reported on the incidence and type of complications occurring in erythremia prior to the use of myelosuppressive agents.[14, 17, 27, 28, 33-35] Thus Stroebel et al.[17] report an incidence of 31.1 per cent hemorrhage and thrombosis, 27 per cent hyperuricemia and 32

per cent leukemoid reactions in erythremia prior to internal radiation therapy. Analysis of the cause of death in this group as well as in others[14, 26] again emphasizes the increased proportion of vascular accidents, 56 per cent of the patients dying of hemorrhage or thrombosis; in our series of patients the direct relation of complications to the hypervolemia and panmyelosis is also apparent (Fig. 5, Fig. 7).

Elevation of the serum uric acid to over 5 mg. per cent in females and 6 mg. per cent in males occurred in 32 (12 per cent) and 57 (21 per cent) respectively, values similar to those reported.[17] Despite the hyperuricemia found in 33 per cent of the cases, gout was a rare complication, occurring or developing in only five (1.9 per cent) of our patients and only two (0.8 per cent) cases of renal calculi were seen. The incidence of gout in erythremia has been reported as somewhat higher varying from 4.7 per cent to 10 per cent[26, 36] with probably a greater number of cases occurring in the spent phase of the disease.[25, 37] One might expect a greater incidence in view of the tremendous cellular catabolic activity with degradation of nucleoprotein to purines and uric acid. The relationship of serum uric acid to the level of red and white blood cells is illustrated in Fig. 6. No particular correlation appears evident, some of the highest red and white cell concentrations showing normal uric acid levels whereas the reverse situation frequently prevailed. Following myelosuppressive therapy as contrasted with the conventional therapy of venesection and hemolytic agents, the serum uric acid, when elevated, invariably returned to normal levels. The fact that high uric acid levels occur with normal red and white blood cell concentrations, and diminish following marrow suppressive therapy, seems to indicate increased proliferation of hematic and non-hematic cells in the marrow with a probable failure of delivery or death of many of the cells produced.

During the course of the disease vascular accidents occurred in 42 per cent of the group, with thrombosis or phlebitis accounting for 26 per cent and hemorrhage 16 per cent (Fig. 5). The latter figure does not include minor hemorrhagic manifestations such as bleeding from the gums or nose, easy bruisability or occasional petechiae but rather hemorrhages severe enough to require medical attention. This high incidence of vascular accidents may be contrasted with results in a group of 128 of our cases treated with radioactive phosphorus or triethylene melamine. In this group, thirty-one instances (24 per cent) of thrombosis and

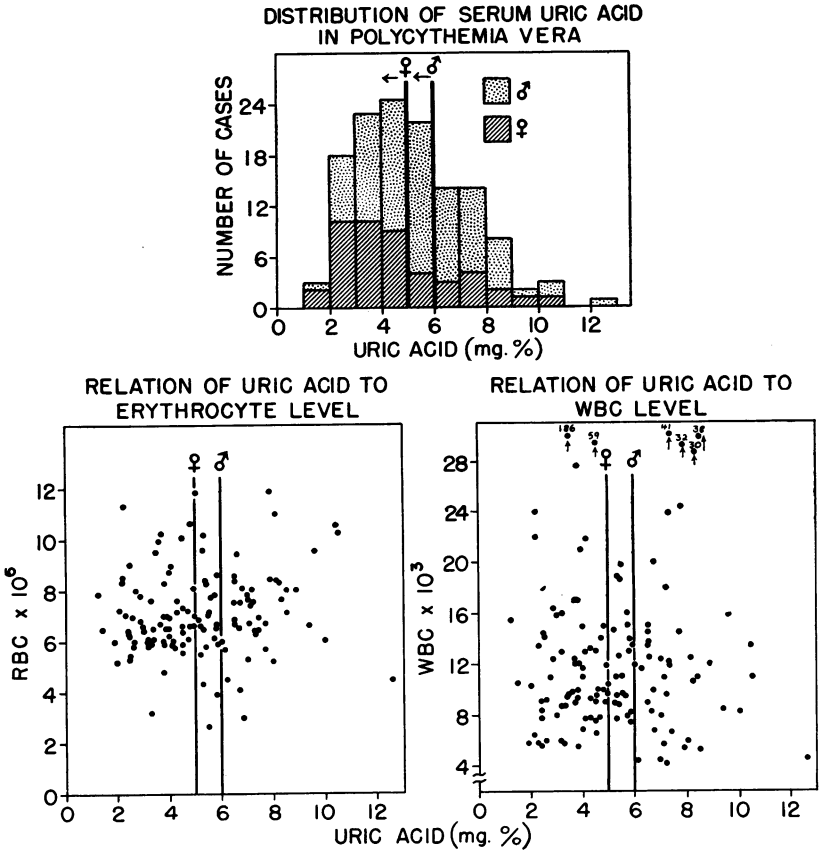

Figure 6: Uric acid levels in polycythemia vera. Note the lack of correlation between hyperuricemia and elevated red and white cell levels.

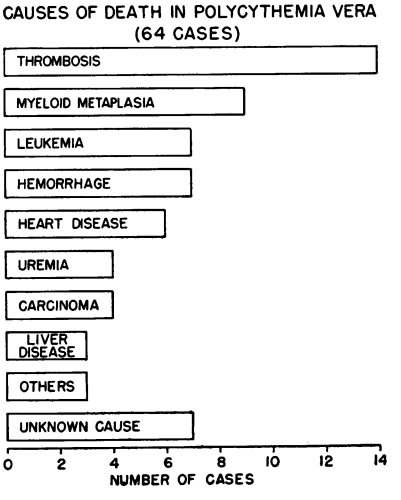

Figure 7: Causes of death in 64 cases of polycythemia vera treated by all forms of therapy. "Leukemia" refers only to the acute type; myeloid metaplasia includes myelofibrosis and all associated pathological entities. Where hemorrhage, thrombosis, etc. occurred as a direct cause of death in advanced myeloid metaplasia, death was classified as being due to myeloid metaplasia only.

twelve (10 per cent) of hemorrhage occurred prior to therapy whereas only seven patients (5.5 per cent) developed thrombotic manifestations and three (2 per cent) showed a hemorrhagic tendency after the use of myelosuppressive agents. Of the seven cases developing thrombosis after treatment, five occurred either in cases difficult to control or inadequately treated.

Peptic ulcer has been reported as occurring in 7 per cent to 20 per cent of patients with polycythemia vera.[14, 26, 29] In our group, 8.6 per cent had definite roentgenologic evidence of gastric or duodenal ulceration although about 50 per cent of the patients complained of gastrointestinal disturbances. Thrombosis of small mesenteric vessels as well as impaired circulation due to the capillary dilatation probably account for the increased incidence of ulcer in erythremia.

Leukemia and myelofibrosis with myeloid metaplasia should not truly be classified as complications but rather as stages of erythremia occurring incident to the natural course and duration of the disease. All patients with polycythemia vera will develop anemia and qualitative and quantitative changes in the white cells and platelets with marrow fibrosis and extramedullary hemopoiesis if they do not succumb to one of the complications noted previously. Chronic myelocytic leukemia was definitely seen in only one patient who finally died of acute myeloblastic leukemia (Fig. 14). The designation of leukemoid and chronic leukemic pictures in erythremia are confusing, the former merely reflecting the myeloid hyperactivity and the latter, heteroplastic blood formation with excessive stimulation of the myeloid cells. Full blown myeloid metaplasia was found in thirteen cases or 8.6 per cent of 150 cases with at least a five year history and seven additional patients (4.7 per cent) developed acute leukemia terminally.

Further analysis of the causes of death in polycythemia vera again demonstrates the dangers of the pancytosis (Fig. 7). Of sixty-four deaths in our group of polycythemia vera cases, vascular accidents accounted for twenty-one or about 33 per cent, thrombosis occurring in fourteen (22 per cent) and hemorrhage in seven (11 per cent). This latter group does not include those dying of hemorrhage in the terminal phases of the disease but rather represents cases of early erythremia without myeloid metaplasia or leukemia.

The next most frequent cause of death occurring in nine patients (14 per cent) was so-called "spent polycythemia" or myeloid meta-

plasia with myelofibrosis. Hemorrhage, infection or cardiac failure is usually present and precipitates the terminal event.

The incidence of carcinoma in this disease, about 6 per cent, does not appear to be any greater than in the general population. Four patients (6 per cent) died of uremia secondary to nephrosclerosis and not associated with renal calculi and hyperuricemia as may occur in the lymphomatous diseases. It is interesting that in the group classified as "others," one patient had extensive tuberculosis with splenic involvement, one multiple myeloma and the third Hodgkin's disease. The occasional association of the latter two diseases has been noted before and lends support to the unitarian concept of the reticuloses.[14, 23] Eight additional patients were known to have died but the direct cause of death could not be ascertained.

The occurrence of leukemia in erythremia as an end result of the natural course of the disease or as a complication of radiation therapy has been the subject of many reports.[13, 14, 22, 26, 27, 35, 38-40] Unfortunately, comparable statistics for large series of cases treated in various ways are not available and careful follow-up studies were practically non-existent prior to the use of internal radiation therapy as supplied by radioactive phosphorus. Seven patients (11 per cent of sixty-four deaths) died with acute myeloblastic leukemia. Treatment in three cases consisted of radioactive phosphorus and phlebotomy, one patient receiving a total of only three millicuries P^{32} two and a half years prior to death. One patient received one course of x-ray to the spleen three years prior to his exitus, treatment otherwise consisting only of venesections. Three cases were treated with venesections, local x-radiation to the long bones or spleen and multiple courses of radioactive phosphorus when it became available. In general, those cases terminating in an acute leukemia were most difficult to control,[17] the erythrocytosis usually being accompanied by a prolonged leukemoid blood picture and marked splenomegaly.

Incidences of leukemia, ranging from 10 to 30 per cent or more, have been noted in erythremia, the majority of cases being of the chronic myelocytic type with only an occasional case of acute leukemia appearing.[14, 27, 39] In the light of present experience wherein seven out of sixty-four or 11 per cent of deaths in our cases of erythremia, 14 per cent as reported by Lawrence,[14, 27] 30 per cent in Wiseman's[15] collected series and 18 per cent in the Mayo group reported by Stroebel[17] were due to acute myeloblastic leukemia, and chronic myelocytic leukemia was seen

as a terminal picture in only four cases of the above combined series, some factor or factors must be implicated.

Twenty-five per cent of the deaths in our series were due to both myeloid metaplasia with myelofibrosis and acute leukemia; 27 per cent of the deaths in Stroebel's group terminally showed acute leukemia, chronic myelocytic leukemia or aplastic anemia and 20 per cent in the series reported by Lawrence were of the same categories. Thus of 144 deaths (sum of above three series) in polycythemia vera treated with x-ray or P^{32}, about 25 per cent were due to leukemia and myelofibrosis. This may be contrasted with the higher combined mortality statistics for acute and chronic leukemia, "aplastic anemia," myelofibrosis and myeloid metaplasia following treatment with venesection, phenylhydrazine or radiation. That acute leukemia can occur as a terminal event in erythremia treated only by venesection was demonstrated recently in two cases followed by Dameshek.[41] Tinney and his associates[42] reported the high incidence of leukemia, as much as 80 per cent, occurring in patients surviving over fifteen years, and emphasized the direct relation between duration of the erythremic state and abnormal white cell proliferation.

The life span of polycythemia vera patients treated with P^{32} as reported by Lawrence[14] far exceeds that of other groups not so treated. A median survival of 13.2 years for polycythemia vera treated with radiophosphorus was found in his group as compared with about 6.7 years noted by Videbaek.[26] It seems reasonable to conclude that through the use of marrow suppressive therapy, the duration of the disease is prolonged and patients who would probably have died at one of the earlier phases of the disease are now being carried to the end stages of erythremia until complete disorganization of hematic cell proliferation occurs.

Reduction in the blood volume, suppression of the increased marrow activity and reduction in the white cells and the platelets are all a necessary feature of any successful treatment of polycythemia vera. The danger of severe hemorrhage or thrombosis always exists and sound therapy should be directed toward rapid amelioration of not only the symptoms but, more important, normalization of the sluggish thrombocythemic blood by means of a marrow suppressing agent. It is not unusual to see coronary thrombosis, cerebral thrombosis or hemorrhage, pulmonary infarction and gastrointestinal hemorrhage occur while

therapy is being contemplated or during the process of adhering to a minimal treatment policy.

At least brief mention should be made of the problem of coagulation and hemorrhage in polycythemia vera. It is paradoxical that despite normal or elevated blood platelets, bleeding at times may be extensive. Death due to exsanguination has occurred in erythremia particularly following surgery.

Patients with erythremia with elevated packed cell volumes and thrombocytosis seem to have poor clot retraction.[43] Clot retraction may actually occur rapidly, but because of the increased red cell volume, only a few red cells are caught in the fibrin mesh, and a tiny but well retracted clot is formed leaving most of the red cells free in the serum thus giving the appearance of poor clot retraction.[44] The bleeding and thrombotic tendency are directly correlated with increased viscosity and red cell mass and thrombocytosis. Again the need for a total myelosuppressive agent in the treatment of this disease is indicated. Further studies in our laboratory by M. C. Rosenthal[45] have indicated all plasma and cellular components now tested for in a bleeding diathesis to be within normal limits. The possibility that reduced plasma concentration results in a relative deficiency of fibrinogen or some other clotting factor could not be substantiated. Similarly the infusion of large amounts of fibrinogen solution intravenously was not successful in stopping or preventing continued hemorrhage in polycythemia vera.

Elective major or minor surgical intervention should not be contemplated unless normalization of the cellular components has occurred. Despite reduction in blood volume these patients may show serious postoperative bleeding[28] directly related to their unusual and complex hemostatic defect. In our group of patients four deaths attributable to exsanguination occurred following surgery despite the reduction in blood volume by hemorrhage and the use of fresh blood, plasma, fibrinogen and local agents.

Necessary elective surgery may be attempted in patients with polycythemia vera after the blood values have been normal for a few months. For those surgical emergencies where slow reduction in blood cells is not possible, venesections plus careful hemostasis should be utilized. Hemorrhage, however, remains an ever threatening problem as does postoperative thrombosis. Again the use of P^{32} or TEM has reduced these complications. Early ambulation and other preventative measures

TABLE III—ANALYSIS OF AGENTS USED IN THE TREATMENT OF ERYTHREMIA

1. P^{32}
   a) Treatment of choice at this time
   b) Effective in over 75% of cases
   c) Dosage must be individualized
   d) Easily administered, no reactions

2. TEM
   a) Nausea & vomiting in 1/3 of cases
   b) Marked variability in response
   c) Minimal effective dose through trial and error
   d) Remissions short-lived
   e) Safety factor small
   f) Results as with P^{32}

3. SPRAY IRRADIATION
   a) Results as with P32
   b) Radiation sickness

4. PHLEBOTOMY
   a) Effect usually rapid but temporary
   b) Iron deficiency produced
   c) Marrow stimulated
   d) Platelets and WBC increase
   e) Circulatory collapse may occur

5. PHENYLHYDRAZINE
   a) Dosage uncertain and variable
   b) Platelets and WBC increase
   c) Marrow stimulated

6. NITROGEN MUSTARD
   a) Variability in response
   b) Remissions short-lived
   c) Severe reactions

7. FOWLER'S SOLUTION
   a) G-I symptoms
   b) Effect variable

TABLE IV—PRINCIPLES OF MANAGEMENT OF POLYCYTHEMIA VERA

1. Rapid reduction of blood volume to normal levels:
   (℞: 300-500cc phlebotomy q 2 days)

2. Suppression of increased marrow activity:
   (℞: P32 intravenously or TEM orally)

3. Maintenance of cellular elements at normal level:
   (℞: CBC q 4-6 weeks)

4. Avoid overtreatment
   ℞: P^{32}—no more than 5-7 mc I.V. in 6 months
   ℞:TEM—start with 10 mg. in first course. Do not repeat for 2 months
   ℞: Phlebotomy in resistant cases

5. Elective surgery contra-indicated unless control established

should be instituted as soon as possible. Anticoagulants are not well tolerated and extensive hemorrhages have occurred following their use; thus heparin, Dicumarol and similar prothrombin reducing agents should be avoided. If anticoagulant therapy is imperative, heparin is the agent of choice.

Until recently the treatment of erythremia had presented a difficult problem. Attempts to bring about a normal physiological state had been directed toward either removal of the excess quantities of blood or the use of a hemolytic agent such as phenylhydrazine[22, 26, 28] (Table III). Neither of these methods was particularly satisfactory since control was difficult and their use indirectly stimulated erythrogenesis. Removal of blood over a prolonged period of time invariably results in an iron deficiency state with production of hypochromic microcytic polycythemia. Although erythropoiesis may be impaired, the other cellular components appear to be stimulated. The serum iron in these cases is exceedingly low and reflects the number of venesections performed. Signs and symptoms of severe iron deficiency such as glossitis, sore mouth and dysphagia have been produced, which respond only to iron therapy. Although the major part of the body iron is in the hemoglobin molecule nevertheless iron is an essential trace element for most metabolic activities and its drastic reduction may seriously impair normal cellular function. When severe iron deficiency is present we have attempted to correct it in conjunction with our usual forms of therapy.

Spray irradiation or deep x-ray therapy to the long bones has been used with success in the treatment of erythremia.[14, 28, 46, 47] As with P^{32} or TEM, because of the relatively slow action of roentgen therapy, prior venesection should be utilized to produce rapid normalization of the blood volume. Frequently, however, radiation sickness may be most uncomfortable to the patient. Where phosphorus or TEM is not available, the use of spray irradiation may be substituted with good results (Table IV).

Triethylene melamine, similar in chemical structure to the active transformation form of nitrogen mustard, is effective when taken orally and is less toxic than HN_2. TEM shows reduced pharmacologic activity at an acid pH, combines readily with organic material but is relatively stable in an alkaline medium and is usually administered in a fasting state with alkali.[48] Although we have used this method of administration exclusively there has been no reduction in the gastrointestinal disturb-

ances, nor in the variability of effects produced. TEM, like HN_2, is a radio-mimetic drug, its cytotoxic action affecting mitotic division. Hence it is most effective in metabolically active tissue such as bone marrow and neoplasia. Suppression of hemopoiesis with reduction in the peripheral cellular elements occurs, and remissions in erythremia have been produced with both oral and intravenous administration of TEM.[49-51]

Thirty-five cases of polycythemia vera have been treated with TEM over the past few years and certain impressions have been obtained. As with P^{32} the "simple" cases, i.e., those not associated with excessive myeloid hyperactivity, respond best.[17] Similarly, early cases appear to benefit more than patients with a long history of the disease. A good response to P^{32} usually indicates a similar response to TEM but the effect of TEM is much more variable, patients responding to one dose once and not thereafter. Small doses of triethylene melamine may be effective and, because of the cumulative effect and the extreme sensitivity of the marrow, readministration in polycythemia vera should not occur for two months. Remissions are short-lived and rarely exceed six to eight months, although one of our patients maintained normal blood values for two years. Side reactions such as nausea and vomiting limit its use in one-third of the patients. The effective dose can only be arrived at through trial and error although a good starting course appears to be 10 mg. in two divided doses over a two or three day period. When radioactive phosphorus is not available TEM may be used with satisfactory results; however, the variable, short-lived remission necessitates much more frequent blood examinations.

The most satisfactory agent thus far introduced for the treatment of polycythemia vera is radioactive phosphorus.[14, 17, 27, 34, 35, 38]

Radioactive phosphorus, P^{32}, (Table III) when administered either orally or intravenously is initially selectively concentrated to some extent in the nucleoprotein of the mitotically active cells in the bone marrow, liver, spleen and tumors.[14, 35, 52, 53] Eventually, depending on the turnover rate of the tissues, the phosphorus is deposited in the large phosphorus pool of the body, the calcium phosphate of bone. The extent of this initial concentration is dependent upon the total exchangeable phosphorus in the tissue, the rate of utilization of the phosphorus and the rate of growth of new tissue.[35] In polycythemia vera not only does the marrow in its hyperplastic state concentrate more than two to three times its usual share of phosphorus but the eventual deposition of the radioactive isotope

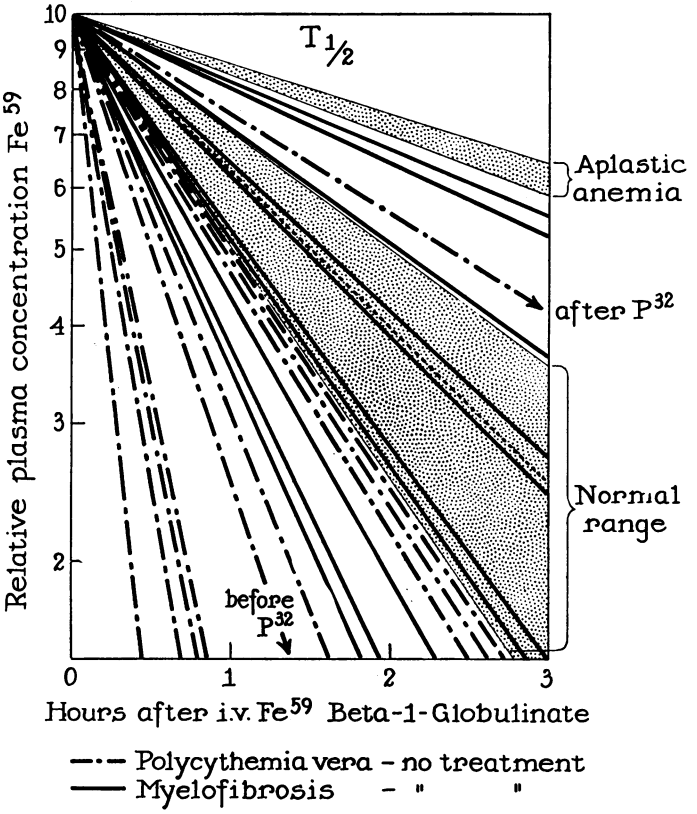

Figure 8: Plasma radioactive iron disappearance in nine patients with polycythemia vera contrasted with the normal and ten cases of myelofibrosis. There is a more rapid clearance of the iron in polycythemia vera signifying increased erythrogenesis. Note the effect of P^{32} in prolonging the half-time of disappearance by the marrow suppressive action of the isotope on erythropoiesis. In myeloid metaplasia the results are variable and approximate the polycythemia values on the one hand and aplastic anemia on the other.

in the bone spicules furnishes added suppressive radiation to the marrow. The desired result of obtaining and maintaining a normal blood picture is achieved by the inhibitory effect of the ionization produced by the beta rays of P^{32} on mitotically active bone marrow cells. This marrow inhibitory effect on erythrogenesis is demonstrated in Figure 8. It has been shown that the half-time of disappearance of intravenously injected radioactive iron, e.g., the time for half of the injected radioactivity to leave the plasma, is a function of erythropoiesis.[1, 2] In normal individuals

FIGURES 9 THROUGH 14: TREATMENT OF POLYCYTHEMIA VERA WITH P^{32} AND/OR TEM (SEE TEXT FOR DISCUSSION OF INDIVIDUAL CASES)

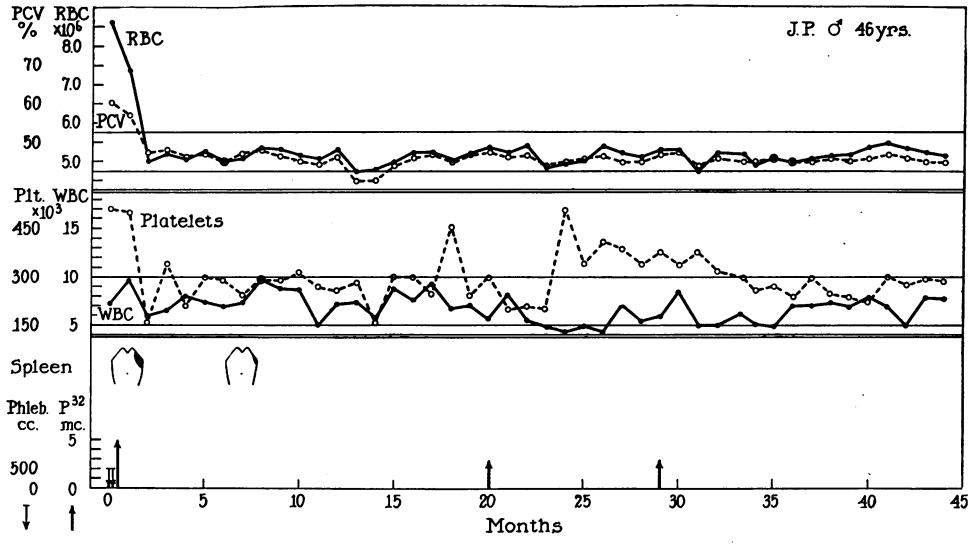

Fig. 9

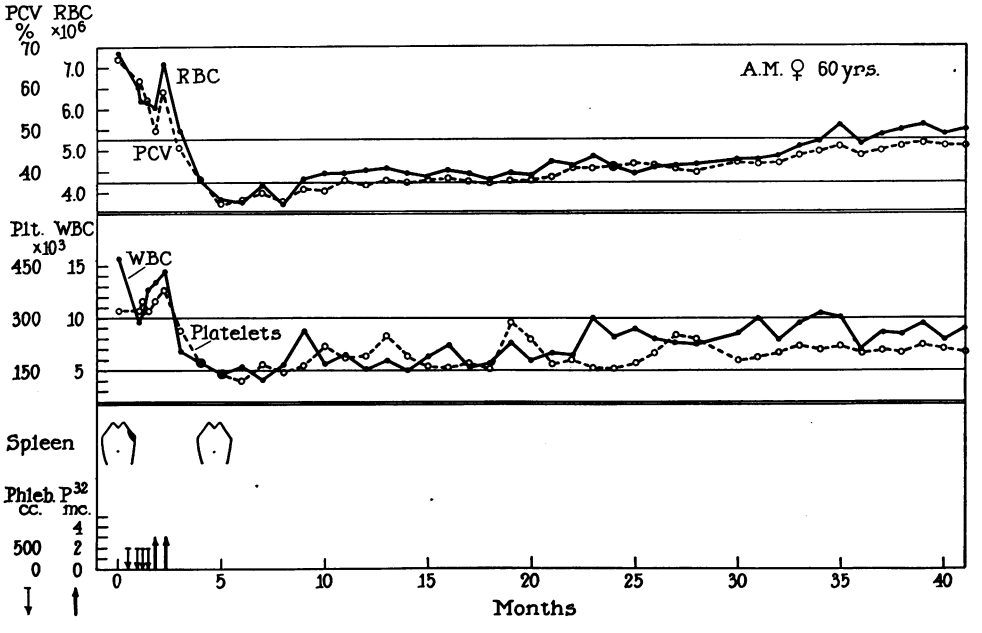

Fig. 10

the half-time of clearance of this iron ranges from seventy to 120 minutes with an average of ninety minutes. Those diseases associated with an empty marrow as in aplastic anemia show a prolongation of the half-time to over 200 minutes, whereas increased erythropoietic activity in the marrow as in polycythemia vera or iron deficiency anemia in a regenerative stage is always associated with an accelerated rate of iron clearance. In nine cases of polycythemia vera tested by this method the half-times ranged from ten to sixty minutes, signifying increased erythroblastic activity in the marrow. The efficacy of marrow suppressive therapy as supplied by radioactive phosphorus in controlling this excessive erythrogenesis is demonstrated by the change in rate of disappearance of the radioiron from a T½ of thirty minutes to a value of 140 minutes, approximating the normal (Fig. 8). With the proper dosage of P^{32} deleterious effects are avoided and the morbidity and mortality associated with untreated or poorly treated polycythemia vera is markedly reduced. Thrombosis and hemorrhage rarely complicate the well treated case of erythremia and it does not appear as if the incidence of leukemia, myelofibrosis and neoplastic disease is increased. Since absorption from the gastrointestinal tract may be irregular and approximately twice the intravenous dose is required orally, we have confined our treatment solely to the intravenous route. Good results, however, have been obtained with oral radiophosphorus therapy.[15]

Figure 9 demonstrates the method of therapy formerly employed by us in most cases of polycythemia vera. This "simple" case of erythremia not accompanied by leukocytosis is the ideal case for treatment with a myelosuppressive agent.[17] Following two venesections totalling 1000 cc. at an interval of three days, the patient was given 5 mc. of P^{32} intravenously. Within two months the platelets and red cell concentration had returned to normal and all symptoms of the disease had disappeared. The maximum reduction in red cells however did not occur until twelve months later. A slow rise in the hematocrit and thrombocytosis and slight recurrence of headaches and dizziness prompted retreatment with 3 mc. P^{32} at twenty months and again nine months later. As can be seen, a hematologic remission has been maintained throughout and splenomegaly has disappeared on minimal doses of P^{32} over a three and a half year period.

More recently we have used 3 millicuries as the initial dose followed in one month by an additional 2 to 3 mc. if necessary. Figure 10 demon-

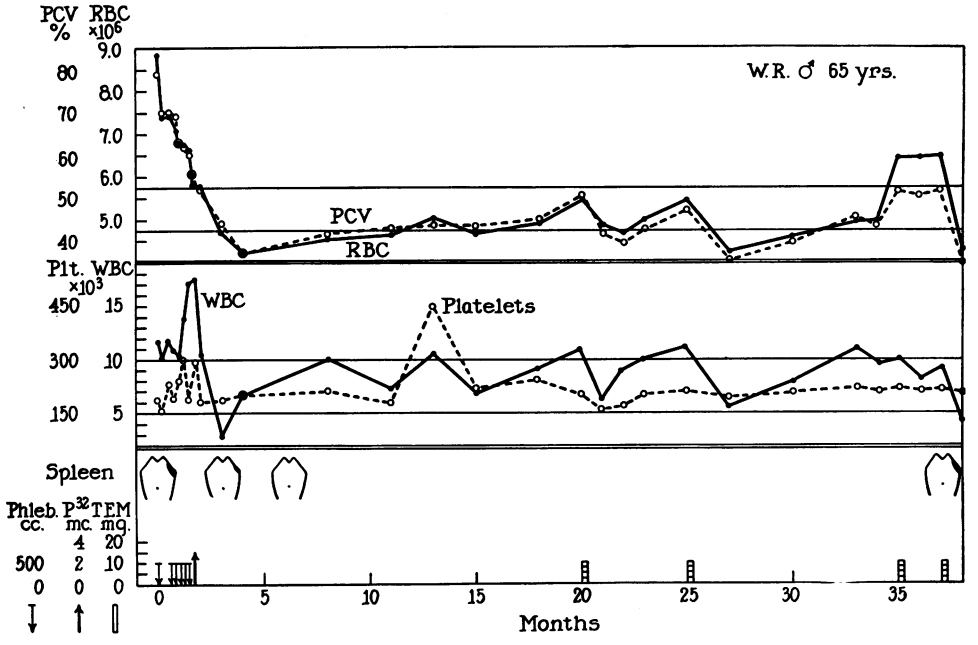

Fig. 11

strates this present method of treatment. Following four venesections at two day intervals totalling 2000 cc. the packed cell volume was reduced from 70 per cent to 47.5 per cent and 3 mc. P^{32} was given intravenously. One month later the hematocrit had again risen to 60 per cent, the white cells and platelets remained elevated and bone marrow aspiration revealed a markedly erythroid marrow similar to the pretreatment sample. An additional injection of 3 mc. was then given. The maximum response occurred two months following the second injection and showed a slight depression of the red cells and platelets below the limits of normal that might have been avoided if a slightly smaller dose had been given at the second injection. Over a period of three and a half years the patient has remained in an excellent clinical and hematologic remission. The blood pressure in this patient has remained persistently elevated in the range of 230/120 despite the excellent response. Little effect on reducing the blood pressure has been noted by us and others following P^{32} or TEM.[14]

The effect of only 3 mc. P^{32} in producing a prolonged remission is illustrated in Fig. 11. Venesections totalling 3000 cc. preceded the dose

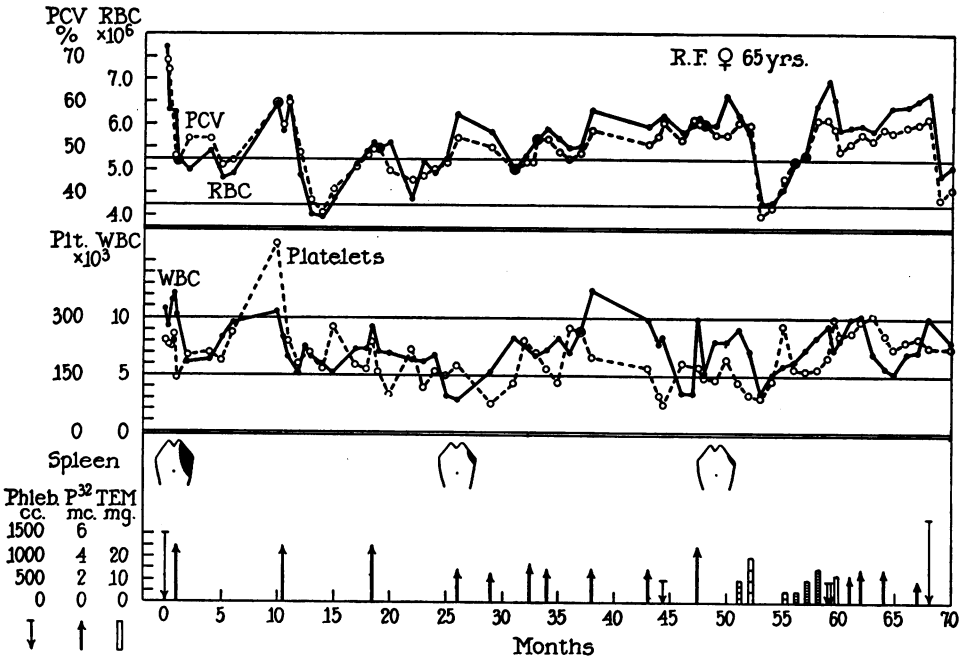

Fig. 12

of radiophosphorus. The maximum response occurred two months later with a slight anemia and leukopenia despite the small dose administered. Note the effect of the venesections in stimulating the white cells. The action of the phosphorus lasted for twenty months when the increasing hematocrit prompted therapy.

TEM was introduced at this time and some of our patients were utilized to evaluate the efficacy of this new drug. The variability in response to similar doses of the drug is well illustrated. The second course of TEM five months after the first produced a greater depression than the initial one and a third course was without effect (Fig. 11). The last dose similar to the others and given after an interval of two months produced a marked drop in the red cells. It is doubtful if this is due to a cumulative effect of the TEM after this period of time. Short-lived remissions, the variability in response and the fear of overtreatment as well as undertreatment following the use of TEM limit one's confidence in the treatment of erythremia with this agent.

Figure 12 demonstrates the marked resistance of some patients to

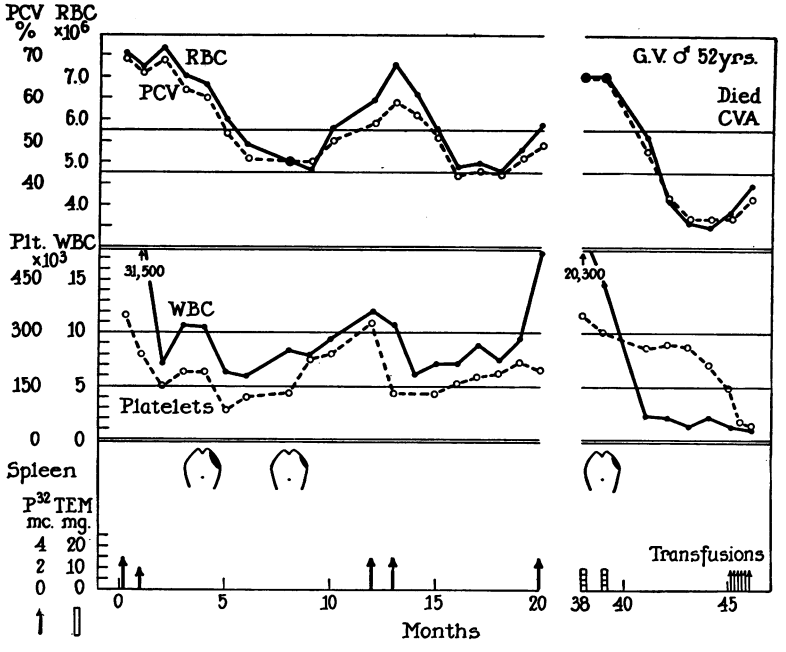

Fig. 13

internal radiation therapy and triethylene melamine. Following three phlebotomies of 500 cc. each, 5 mc. P^{32} produced a maximum response in four months that lasted only two months. Subsequent doses of 3 to 5 mc. at one to five month intervals were ineffective in producing a satisfactory remission. The low level of platelets after the third dose of P^{32} necessitated caution in therapy despite the fact that larger doses of 5 mc. had produced more satisfactory responses. After four years of unsuccessful P^{32} therapy, TEM was tried. The usual initial small doses of 2.5 mg. per day for four days were ineffective but 5 mg. daily doses totalling 20 mg. produced a temporary remission; intolerance to the larger amounts necessitated a reduction to daily 1 mg. doses which also provoked severe nausea and vomiting. Radioactive phosphorus in 2 to 3 mc. doses was again tried with no response. Finally coronary thrombosis occurred and treatment with daily small venesections of 100 to 200 cc. was instituted. The patient is now maintained at normal blood values with frequent phlebotomies and small doses of P^{32} will be administered as needed to maintain normal platelet levels (Fig. 12). In retrospect, myelosuppressive therapy should have been discontinued when the red cell levels could

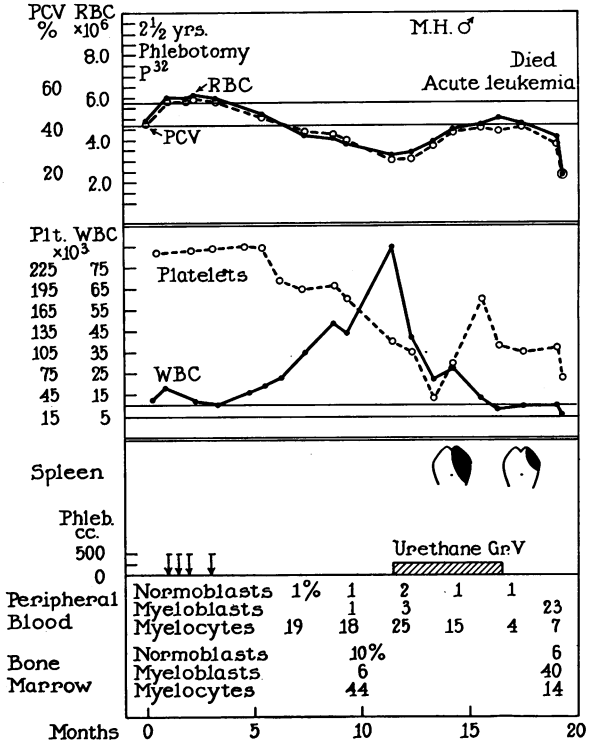

Fig. 14

not be controlled in the face of thrombopenia and leukopenia and venesection instituted as needed.

The danger that accompanies treatment with TEM is well illustrated in Fig. 13. P^{32} was relatively effective in maintaining normal blood values for six to eight months, this despite initial high white cell and platelet levels. An initial dose of 3 mc. P^{32} was followed in one month by 2 mc. of radioactive phosphorus. Retreatment with small doses was necessary twelve months later and again a temporary remission was obtained. After an absence of one and a half years the patient returned and TEM was given with disastrous results. A small dose of TEM, 10 mg. in 2.5 mg. daily divided doses was ineffective and hence one month later the same dose was readministered. A continued fall in all the cellular elements occurred and despite multiple transfusions and antibiotics, a fulminating pneumonia and finally hemorrhage caused death (Fig. 13). Only two 10 mg. courses spaced one month apart were sufficient to precipitate

this fatal episode. At the present time retreatment is never given before eight weeks have elapsed following a previous dose of TEM.

A blood picture indistinguishable from chronic myelocytic leukemia was seen in only one of our cases (Fig. 14). This male, aged fifty-five, had received 3 mc. P^{32} two and a half years previously and had been subsequently controlled by biweekly or monthly venesections. After a polycythemic phase of only three years, the red cells began to fall with a rise in the white cells and the appearance of numerous myelocytes and an occasional normoblast in the peripheral blood. Examination of the bone marrow revealed the myelocytic hyperplasia seen in chronic leukemia but splenic aspiration demonstrated the picture of myeloid metaplasia. Nevertheless the patient was treated as a chronic myelocytic leukemia with urethane for about five months (Fig. 14). A dramatic response in well-being as well as in the blood occurred. The red cells rose and the white cells fell to normal levels and only an occasional myelocyte could be seen on the smears. Urethane was discontinued when the count was normal and symptoms had disappeared. Within a few months, however, the red cells were noted to drop to four million and within one month thereafter the picture of an acute myeloblastic leukemia appeared. Without treatment during the chronic myelocytic stage this patient might have died at that time. With anti-leukemic therapy death was probably postponed until the disease had run its natural course and a maturation arrest in the white cells produced a terminal acute blastic picture. Post-morten examination revealed focal extramedullary hematopoiesis, leukemic infiltrations in all the organs and spotty myelofibrosis. Despite statements to the contrary, myeloid metaplasia with myelofibrosis may be treated with anti-leukemic agents. In four patients we have utilized small doses of splenic radiation with relief of pressure symptoms as well as improvement in the blood picture. Chemotherapy as demonstrated in the case presented above was also successful for a short while in improving the clinical and hematologic status.

Certain principles for the satisfactory treatment of polycythemia vera have been successfully used during the past ten years (Table IV). Initial rapid reduction of the blood volume followed by radioactive phosphorus has given the most satisfactory results. Frequent follow-up visits are essential to maintain normal blood values. Marrow suppressive therapy must be administered cautiously and must be individualized,

particularly when TEM is used because of its greater variability in response. A lack of response in the red cells with depression of the white cells or platelets usually indicates that myelosuppressive therapy should be terminated and venesections utilized thereafter. Elective surgery should not be contemplated unless control of the blood has been established for at least one month.

Although radiation is not the final answer for any treatment, until the etiology of erythremia is known, the marked reduction in morbidity and the ease of administration associated with the use of P^{32} make radioactive phosphorus the treatment of choice in polycythemia vera.

Summary

1. A dynamic concept of polycythemia vera is presented encompassing the various clinical and pathological features encountered during the course of the disease.

2. Polycythemia vera may well be a reticulosis with an initial manifestation in increased erythrogenetic activity; simultaneous and subsequent stimulation of other hematic and non-hematic mesenchymal derivatives will produce the complex syndromes seen in erythremia.

3. The relationship of polycythemia vera and myeloid metaplasia is discussed.

4. The complications in erythremia are directly related to the hypervolemia and panmyelosis.

5. The hemorrhagic diathesis found in polycythemia vera is due to a complex hemostatic defect; elective surgical intervention should thus be avoided unless normal blood values have been achieved.

6. The therapy of polycythemia vera is discussed; radioactive phosphorus remains the treatment of choice in this disease.

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